DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Jennifer Richards
Associate Director, Regulatory Affairs
Salix Pharmaceuticals, Inc.
8510 Colonnade Center Drive
Raleigh, North Carolina 27615

Lisa Conte
Chief Executive Officer
Napo Pharmaceuticals, Inc.
185 Berry Street, Suite 1300
San Francisco, CA 94107

RE: (b) (4)
Crofelemer tablets
MA #2

Dear Ms. Richards and Ms. Conte:

This letter notifies Salix Pharmaceuticals, Inc. (Salix), and Napo Pharmaceuticals, Inc. (Napo), that, as part of its monitoring and surveillance program, the Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed Napo's company website[1] and statements made by Napo Chief Executive Officer Lisa Conte, during an interview, available as a podcast[2] regarding Crofelemer tablets (crofelemer). The website and podcast contain claims that promote crofelemer, an investigational new drug, as safe and effective for the purposes for which it is being investigated. As a result, the website and podcast violate the Federal Food, Drug, and Cosmetic Act (the FD&C Act) and FDA implementing regulations. 21 CFR 312.7(a).

Background

Crofelemer is an investigational new drug that does not have marketing authorization in the United States. (b) (4) According to a news release by Napo, Salix "has licensed the commercial and development rights to crofelemer for all indications

[1] http://www.napopharma.com/ (last accessed November 27, 2012)
[2] "The Long Journey from the Amazon to the FDA," March 5, 2012, *available at* The Burrill Report website http://www.burrillreport.com/article-4345.html (last accessed November 27 , 2012)

in North America . . . ."[3] In a subsequent news release,[4] Napo announced that it had terminated its agreement with Salix. However, Salix has taken the position that the "purported termination of the license is groundless and without merit" and continues to assert that the company "has an exclusive license [from Napo] to the HIV–associated diarrhea indication for Crofelemer and the additional indications of pediatric diarrhea and acute infectious diarrhea in North America."[5]

Promotion of an Investigational Drug

Promotion of an investigational new drug is prohibited under FDA regulations at 21 CFR 312.7(a), which states that "A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution."

The website and podcast contain claims such as the following that promote crofelemer as safe and/or effective for the purposes for which it is being investigated or otherwise promote the drug:

Website

Crofelemer – CRO-PED section

- "Safety in children in the US as young as 3 months and appropriate mechanism for population"

Crofelemer – Mechanism of Action section

- "Crofelemer does not affect gut motility and is not absorbed systemically to any significant level, two important characteristics associated with the product's demonstrated safety profile and suitability for chronic administration"

- "Since crofelemer specifically blocks the mechanism by which many bacterial toxins produce diarrhea, it is ideally suited to treat the secretory diarrhea produced by acute bacterial infections (traveler's diarrhea and cholera infection)."

- "Crofelemer also targets the primary cause of secretory diarrhea associated with some drugs, specifically those used to treat HIV/AIDS."

[3] http://www.napopharma.com/news/FINAL_ADVENT_Results.pdf
[4] http://www.napopharma.com/news/Napo_Terminates_Salix.pdf
[5] http://www.salix.com/news-media/news/index/salix-pharmaceuticals-announces-nda-submission-for-crofelemer-for-the-treatment-of-hiv-associated-diarrhea.aspx (last accessed Nov. 27, 2012).

- "This mechanism of action and safety profile provide a strong rationale for treatment of diarrhea in children, for whom there are currently only limited therapeutic options."

Podcast – During the podcast, in response to the interviewer's questions, Ms. Conte states the following in word or substance:

- I call it a normalizer [pause], what it does, is it normalizes the abnormal ion flow that comes into the gut . . . and by normalizing the ion flow you normalize the water flow; and it does so without interfering with peristaltic activity so you don't cause constipation . . . . And that's opposed to what we think of with Imodium or loperamide, other agents that we take that work basically by the mechanism of constipation, so they can't be used on a chronic basis and they can be particularly unsafe in young children or if you have a particularly noxious or toxic infectious agent.

- This product has so many different indications because the mechanism of action is a basic normalizing, it's sort of the holy grail, the last step in the basic functional mechanism of action. So, it [Crofelemer] works for diarrhea in AIDS patients . . . it works for cholera patients, it works for the most severe acute, infectious, watery diarrhea, works for the most mild diarrhea . . . .

These claims suggest that crofelemer is safe and/or effective for the treatment of various types of diarrhea, including: AIDS diarrhea; traveler's diarrhea; diarrhea due to cholera infection; severe acute, infectious, watery diarrhea; and, mild diarrhea. Furthermore, these claims suggest that crofelemer is safe and/or effective for the treatment of pediatric patients as young as three months.

Since crofelemer is an investigational new drug, the product's indication(s), warnings, precautions, adverse reactions, and dosage and administration, have not been established and are unknown at this time. Promoting crofelemer as safe and effective for purposes for which it is under investigation by making representations such as those noted above violates 21 CFR 312.7(a).

Conclusion and Requested Action

For the reasons discussed above, the website and podcast violate the FD&C Act and FDA implementing regulations. 21 CFR 312.7(a). These statements are concerning from a public health perspective because they make promotional claims about the safety and efficacy of an investigational new drug that has not been approved by the FDA.

OPDP requests that you immediately cease the dissemination of violative promotional materials for crofelemer such as those described above. Please submit a written response to this letter on or before December 11, 2012, stating whether you intend to comply with this request, and explaining your plan for discontinuing use of such violative materials.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, Division of Professional Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266** or by facsimile at (301) 847-8444. Please note that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has been reorganized and elevated to the Office of Prescription Drug Promotion (OPDP). OPDP consists of the Immediate Office, the Division of Professional Drug Promotion (DPDP) and the Division of Consumer Drug Promotion (DCDP). To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. In addition, OPDP recently migrated to a different tracking system. Therefore, OPDP letters will now refer to MA numbers instead of MACMIS numbers. Please refer to MA #2 in addition to the NDA number in all future correspondence relating to this particular matter. OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your materials for crofelemer comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Kathleen Klemm, Pharm.D.
Regulatory Review Officer
Division of Professional Drug Promotion
Office of Prescription Drug Promotion

{See appended electronic signature page}

Lisa Hubbard, R.Ph.
Team Leader
Division of Professional Drug Promotion
Office of Prescription Drug Promotion

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/s/

EUNICE H CHUNG-DAVIES on behalf of KATHLEEN KLEMM
11/27/2012

LISA M HUBBARD
11/27/2012